Barts and The London
School of Medicine and Dentistry

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

HARBIGE et al — Atty. Ref.: 604-706; Confirmation No. 1504

Appl. No. 10/756,761 — TC/A.U. 1627

Filed: January 14, 2004 — Examiner: Kantamneni, Shobha

For: TREATMENT OF NEURODEGENERATIVE CONDITIONS

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Gavin Giovannoni, declare and state that:

1. I am a Professor of Neurology at the Blizard Institute of Cell and Molecular Science, associated with Barts and The London School of Medicine and Dentistry, located in London, England.

2. I specialize in the study of multiple sclerosis (MS) and other inflammatory disorders of the central nervous system. I am interested in clinical issues related to optimizing MS disease modifying therapies. In one aspect, my research focuses on Epstein Barr virus as a possible cause of MS, MS related neurodegeneration, MS biomarker discovery, MS clinical outcome measures, MS clinical trials and immune tolerance strategy.

3. I have reviewed Lunardi *et al.*, Neurology, Vol. 48(6), 1997, pp1714-1717, and the Bountra *et al.* patent application (WO0061231) (Bountra).

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4. Prior to the present invention, the recommended daily maximum dosage of lamotrigine (LTG) in the treatment of MS was 400mg daily.

5. Lunardi and colleagues treated 15 patients with trigeminal pain with LTG of which 5 patients had MS (patients 16-20). Of the five patients with MS, the highest dose used was 200mg/day (patient 17).

6. I understand that the assertion is made that a physician treating MS patients would have taken at face value the statement at page 10, lines 3-7 of Bountra, in regard to dosage levels of LTG, that:

> "A suitable dose is for example 0.1 mg/kg to 30 mg/kg body weight per day calculated as the free base, for example 3 mg/kg to 15 mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900 mg per day."

7. In response, it is my opinion that, at the time of the present invention, an experienced neurologist in this art such as myself would not have contemplated administering LTG to a patient suffering from MS in dosage levels higher than the recommended maximum of 400mg daily. My reasoning is as follows.

8. LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above, i.e., greater than 4X the anticonvulsant dose in rats (although the ED50 is 2mg/kg, the rat anticonvulsant ED95 is approximately 5mg/kg – for a further discussion on anticonvulsant doses and neuroprotective doses of LTG, see: *The Mechanisms of Action of Lamotrigine,* Meldrum and Leach, 1994, Rev. Contemp. Pharmacother. 5:107-114).

9. In rat middle cerebral artery occlusion (MCAO) model studies published by Smith and Meldrum in 1995 (*Cerebral protective effect of lamotrigine after focal ischemia in rats,* 1995, Stroke:26,117-122), LTG is only neuroprotective in this model of focal ischemia over a narrow

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dose range. In fact, only a dose of 20mg/kg IV significantly reduced neurological scores. The paper concludes:

> "Lamotrigine exhibits a bell-shaped dose-response curve for cerebroprotective effect after MCA occlusion in rats. The optimally effective dose is 20mg/kg, which is 10 fold the anticonvulsant dose in rats (anticonvulsant ED50 values against maximal electroshock-induced or sound- induced seizures are 2mg/kg)".

10. Doses of LTG (10-50mg/kg) higher than anticonvulsant doses have been used in other studies of global ischemia to achieve neuroprotection in gerbil, rat and pig (see *Lamotrigine: Mechanisms of Action.* Leach, Randall, Stefani and Hainsworth, 2002, In: Antiepileptic Drugs, 5th edition, Eds. Levy, Mattson, Meldrum, Perucca).

11. The minimum effective LTG concentration to block white matter ischaemia *in vitro* is 100μM (*Mechanisms of ischaemic damage to central white matter axons: a quantitative histological analysis using rat optic nerve*, Garthwaite *et al.*, Neuroscience, 1999, 94:1219-1230). A usual adult maintenance dose for LTG monotherapy of 100-200mg daily with plasma concentrations around 2-4μg/ml (8-16μM) is far lower than concentrations of LTG to reduce white matter axonopathy.

12. Doses of LTG lower than 400mg per day have been used to treat central pain in patients with MS. In the paper by Leandri and colleagues (*Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis*, Leandri *et al.*, 2000. iNeurol. 247:556-558), doses of 25mg daily to a maximum of 400mg daily were used.

13. Pain due to trigeminal neuralgia in patients with MS is usually due to an inflammatory plaque in the root entry zone of the trigeminal nerve and is typically responsive to anti-convulsant medications within the recommended dose ranges, including that for LTG (<400mg per day).

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14. It is important to note that the indication in this context is for trigeminal neuralgia or pain and **not** neuroprotection, which was not investigated in these studies.

15. Doses that work against central pain syndromes appear to be similar to typical anti-convulsant doses and are typically lower than doses employed for neuroprotection.

16. Given the published facts prior to the present invention and subsequent US 2004 patent filing, it is surprising to me and would not have been obvious to me (or any other neurologist with skill in the art of administering LTG) that doses higher than the recommended maximum of 400mg daily could be effective to modify the course of the progressive pathology of MS to the extent exhibited in the patent application.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Gavin Giovannoni

17 - MAY - 2010

Date